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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/015,989	12/10/2001	Andrew Darrow	ORT-1552	3866

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EXAMINER	
MOORE, WILLIAM W	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 03/09/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/015,989	DARROW ET AL.	
	Examiner	Art Unit	
	William W. Moore	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-26* is/are pending in the application.

4a) Of the above claim(s) *1-10 and 13-26* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *11 and 12* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-26* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/01, 11/02, 2/04*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Information Disclosure Statement

Information Disclosure Statements [IDS] filed with the application on 01 December 2001 and on 25 November 2002 are redundant, thus many citations in the former are lined-through to prevent duplication on the face of a patent issuing on this application. Three incomplete citations in both IDS, lacking one or more of a journal designation, a complete title, and page numbers, and these are also lined-through in the latter IDS.

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. § 121:

I. Claims 1-7 and 19-21, drawn to expression vectors, kits and compositions comprising same, recombinant host cells comprising same, and methods of making an encoded product utilizing same, classified, *inter alia*, in class 435, subclass 320.1.

2. Claims 8-10 and 22-26, drawn to a serine protease catalytic domain, pharmaceutical and non-pharmaceutical compositions comprising same, and methods of in treating dermatological conditions using the former, classified in class 435, subclass 226.

3. Claims 11 and 12, drawn to a method of use of a serine protease catalytic domain in an assay to identify modulatory compounds, classified in class 435, subclass 23.

4. Claims 13-18, drawn to compounds capable of modulating the activity of one of six disclosed serine protease catalytic domains, pharmaceutical compositions comprising same, and methods of use of the compositions in treating a medical condition, classified in class 530, subclass 300.

Inventions of Group 1 and Group 2 are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP §

808.01). In the instant case the different inventions are independent chemical entities and require separate searches in the patent and non-patent literature.

The invention of Group 1 is unrelated to inventions of Groups 3 and 4. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case, the method of Group 3 does not utilize the vector of Group 1 and the compounds of Group 4 are independent chemical entities structurally unrelated to the vector of Group 1.

Inventions of Group 2 and Group 3 are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the protease domain of Group 2 can be used in a different method such as a method of making an antibody.

The inventions of Group 2 and Group 4 are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are independent chemical entities having different functions and structures.

The inventions of Group 3 and Group 4 are unrelated. Inventions are unrelated if it can be shown that they are not disclosed as capable of use together and they have different modes of operation, different functions, or different effects (MPEP § 806.04, MPEP § 808.01). In the instant case the different inventions are not disclosed as

capable of use together and they have different modes of operation, different functions, or different effects.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification, restriction for examination purposes as indicated is proper.

During a telephone conversation with Mr. Michael D. Ruse, Jr. on 24 January 2005 a provisional election was made **with** traverse to prosecute the invention of Group 3, claims 11 and 12. Affirmation of this election must be made by applicant in replying to this Office action. Claims 1-10 and 13-26 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Notice of Requirements for Rejoinder

The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier.** Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined claims must meet all criteria for patentability including the requirements of 35 U.S.C. §§101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. §121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

Claim Objections

Claims 11 and 12 are objected to because of the following informalities: Claims 11 and 12 ultimately depend from claims 1 and 4 but must be rewritten in independent form to incorporate the limitations of claims 1 and 4. Thus claim 11 would, if amended in response to the following rejections, may incorporate such limitations by reciting, by way of example, "[a] method for identifying compounds that inhibit the proteolytic activity of a serine protease catalytic domain, the method comprising

(a) preparing an expression vector comprising a polynucleotide encoding a fusion polypeptide comprising an exogenous pro-sequence and a protease catalytic domain and transforming a host cell with the vector;

(b) expressing the fusion polypeptide in the host cell;

(c) isolating the fusion polypeptide and providing conditions permitting cleavage of the protease catalytic domain the prosequence;

(d) contacting the protease catalytic domain with a labeled protease substrate in the presence of a candidate inhibitor molecule; and,

(e) measuring a change in the amount of labeled substrate;

whereby a change in the amount of the substrate indicates the extent of inhibition of the proteolytic activity of the catalytic domain."

Appropriate correction is required.

Claim Rejections - 35 USC § 101

35 U.S.C. § 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 11 and 12 are rejected under 35 U.S.C. § 101 because the claimed invention lacks patentable utility.

A claimed invention must posses a specific, substantial and credible *in vitro* or *in vivo* utility, but the instant application cannot identify any specific, substantial, utility for

the invention described by the claims known to the inventors at the time the application was filed. While the specification teaches that the catalytic domains of prior art human serine proteases prostasin, neuropsin, protease O, protease F, and the MH2 protease - present in carboxyl-terminal regions of the amino acid sequences of SEQ IDs NOs:11-15, 53 and 54 - are useful in detergent compositions and in topical pharmaceutical, essentially cosmetic, compositions the only use it suggests for an inhibitor detected by the methods of claims 11 and 12, at pages 29-30 of the specification, is inhibition of the proteases *in vivo*, via a pharmaceutical composition. Neither the prior art of record or the specification disclose any *in vivo* utility, however, for inhibitors of these proteases because of which are disclosed in the prior art to be expressed in the human epidermis or dermis, thus use in topical pharmaceutical compositions are not a credible utility for inhibitors detected by the claimed methods. Neither do the specification or prior art describe any physiological, or even artificial, substrate for any of the proteases of SEQ IDs NOs:11-15, 53 and 54 and both the prior art nor the specification fail to describe any particular cellular or physiological role for any protease of SEQ IDs NOs:11-15, 53 and 54. Because there is no disclosure of any specific *in vivo* or *in vitro* utility for an inhibitor that might be identified by a claimed method by Applicant or the prior art of record, no disclosure of a substrate recognized and cleaved by a disclosed protease *in vivo* or *in vitro*, and no disclosure of any specific cellular or extracellular function for disclosed protease that an inhibitor, or "modulator" might be expected to affect, claims 11 and 12 lack utility. A method of use of a material for further research to determine, e.g., its specific biological role, thus identifying or confirming a "real world" context for its use, cannot be considered to be a "substantial utility". *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (Sup. Ct. 1966). Mere allegations of a prospective, potential, utility for a

method of identifying inhibitors having no specific application cannot rise to the level of a credible assertion of a specific and substantial utility.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 11 and 12 are also rejected under 35 U.S.C. § 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims 11 and 12 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification fails to exemplify or describe the practice of a method for detecting compounds capable of enhancing or increasing the catalytic activity of a serine protease catalytic domain. Indeed, methods of detecting molecules that enhance or increase the catalytic activity of native serine proteases are not known in the art. "While one does not need to have carried out one's invention before filing a patent application, one does need to be able to describe that invention with particularity" to satisfy the description requirement of the first paragraph of 35 U.S.C. § 112. *Fiers v. Revel v. Sugano*, 25 USPQ2d 1601, 1605 (Fed. Cir. 1993). The specification's treatment of the claimed subject matter is considered to be entirely prospective where skilled artisans in the relevant field of molecular biology could not predict the nature, structure, or other properties of candidate compounds to select for screening in order to detect or identify a molecule that enhances or augments the catalytic activity of a serine protease.

Claims 11 and 12 are rejected under 35 U.S.C. §112, first paragraph, because the specification, while being enabling for the practice of a method of identification utilizing a native serine protease catalytic domain,
does not reasonably provide enablement for practice of a method of identification utilizing any and all "functional derivatives" of catalytic domains of the human prostasin, the human neuropsin, the human protease O, the human protease F, or the human MH2 protease. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

Claim 11 contemplates the practice of an identification method wherein a protease catalytic domain, according to page 13 of the specification, is a "functional derivative" of any of the native catalytic domains disclosed herein as SEQ IDs NOs: 11 and 12 (both human prostasin), 13 (human neuropsin), 14 (human protease O), 53 (human protease F) and 54 (human MH2 protease), comprising an arbitrary assignment of any or all of amino acid substitutions, additions, or deletions within. The specification, however, cannot support the introduction of undisclosed amino acid insertions, deletions, or substitutions anywhere, in any combination or any pattern, in the native prostasin, neuropsin, protease O, protease F, or protease MH2 catalytic domains. Claims 12 is subject to this rejection in view of its dependency from claim 9. Mere sequence perturbation will not enable the design and preparation of nucleotide sequences encoding a myriad of divergent polypeptides and provide the public with a nucleotide sequence encoding a product that retains a recognizable function.

It is well settled that 35 U.S.C. §112, first paragraph, requires that a disclosure be sufficiently enabling to allow one of skill in the art to practice the invention as claimed without undue experimentation and that unpredictability in an attempt to practice a claimed invention is a significant factor supporting a rejection under 35 U.S.C. §112, first paragraph, for non-enablement. See, *In re Wands*, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) (citing factors relevant to the analysis of enablement). The standard set by the CCPA, the predecessor of the present Court of Appeals for the Federal Circuit, is not to "make and screen" any and all possible alterations because a reasonable

correlation must exist between the scope of guidance provided by the specification and the scope asserted in the claimed subject matter. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 25 (CCPA 1970) (scope of enablement varies inversely with the degree of unpredictability of factors involved in physiological activity of small peptide hormone); **see also**, *Ex parte Maizel*, 27 USPQ2d 1662, 1665 (Bd. Pat. App. & Int. 1992) (functional equivalency of divergent gene products not supported by disclosure of a single B-cell growth factor allele). The Federal Circuit approved this standard set by the CCPA in *Genentech, Inc. v. Novo-Nordisk A/S*, 42 USPQ2d 1001 (Fed. Cir. 1997). Applying the factors discussed in *Wands*, *supra*, to Applicant's disclosure, it is apparent that:

- the specification lacks adequate, specific, guidance for altering amino acid sequences of the five disclosed human proteases' catalytic domains,
- the specification lacks working examples wherein any of the five disclosed human protease catalytic domains herein are altered,
- in view of the prior art publications of record herein, the state of the art and level of skill in the art do not support such alteration, and,
- unpredictability exists in the art where no portions of catalytic domains of members of the S1 class of proteases represented by the amino acid sequences of the five disclosed human proteases have been specifically identified for alteration.

Thus the scope of a claimed method is unsupported by the present specification, even if taken in combination with the teachings available in the prior art. Limitation of the subject matters as indicated in the statement at lines 6-9 of page 3 above is required in order to overcome this rejection.

The following is a quotation of the second paragraph of 35 U.S.C. § 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 11 and 12 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 11 is indefinite in reciting "a protease expressed from the expression vector of claim 4" because the specification teaches that the inhibitor identification method is not practiced with the "protease" encoded by the DNA encoding the fusion polypeptide comprising a "pre", or signal, sequence, a "pro", or propeptide, sequence and a catalytic domain of desired protease of claim 1 which is maintained by the expression vector of claim 4. Instead, the specification teaches that the protease used in the method claim 11 attempts to describe is the catalytic domain itself, without the amino-proximal "pre" and "pro" regions that would be expressed in fusion polypeptide. Claim 12 is included in this rejection because it depends from claim 11 but does not resolve the ambiguity of the recitation of claim 11.

Conclusion

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to William W. Moore whose telephone number is now 571.272.0933. The examiner can normally be reached between 9:00AM and 5:30PM EST. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapura Achutamurthy, can now be reached at 571.272.0928. The fax phone number for all communications for the organization where this application or proceeding is assigned is now 571.273.8300. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is now 571.272.1600.

William W. Moore
3 March 2005

PONNATHAPU ACHUTAMURTHY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. §103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. §103(c) and potential 35 U.S.C. §§102(e), (f) or (g) prior art under 35 U.S.C. §103(a).

Claims 11 and 12 rejected under 35 U.S.C. §103(a) as being unpatentable over Bang et al., U.S. 5,196,355, Kopetzki et al., WO 97/47737, Moloney et al., WO 98/49326, and Kuhn et al., **Gene**, Vol. 162, pp. 225-229, all made of record with Applicant's Information Disclosure, in view of Cohen et al., US 6,232,456, made of record herewith.

Claims 11 and 12 do not require the expression of any particular protease catalytic domain as part of a fusion polypeptide encoded by a vector of the non-elected claim 4 for practice of a claimed method of identification. Bang et al. teach the preparation of an expression vector, termed pLPC, that comprises a DNA sequence encoding a fusion polypeptide comprising, from amino-terminus to carboxyl terminus, a signal region, a propeptide region, and a human serine protease catalytic domain. See cols. 7-14, 17-22, and 27-47. Kopetzki et al. teach the preparation of an expression vector comprising a polynucleotide encoding a fusion polypeptide having signal and propeptide regions both heterologous to an adjacent human serine protease catalytic domain, wherein the vector provides an in-frame cloning site for the insertion of the catalytic domain, as well as a process for the expression of the zymogen form by transferring the vector into suitable host cells and culturing the cells under conditions suitable for recovering the

catalytic domain functioning as a serine protease upon cleavage of the heterologous amino acid sequence regions. See pages 2-16, and 20-26. Kuhn et al. teach the preparation of an expression vector providing a polyhistidine tag in frame with any desired polypeptide for expression of fusion polypeptides comprising the polyhistidine tag in order to facilitate purification of the fusion polypeptide by Ni-NTA agarose affinity chromatography. See Figure 3. Moloney et al. similarly teach the preparation of an expression vector comprising a DNA sequence encoding a fusion polypeptide comprising a signal sequence and a propeptide sequence heterologous to an adjacent human serine protease catalytic domain having an in-frame cloning site for the insertion of the catalytic domain at pages 4-20 and particularly teach a process for the expression of the zymogen and an assay for identifying compounds capable of modulating the expression of the protease at page 14. Cohen et al. teach a method for identifying compounds capable of inhibiting the catalytic activity of a human S1 serine protease by combining the protease, a candidate inhibitor and a chromogenically- or fluorogenically-labeled peptide substrate in solution and then measuring a change in the color or fluorescence resulting from cleavage of the substrate to identify inhibitors of the protease. See Example 20 at columns 66-67.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to prepare an expression vector capable of providing a human S1 protease catalytic domain according to the limitations of claim 4 for use in a method of claims 11 and 12 because Cohen et al. teach that it is important to discover physiologically active inhibitors of human S1 serine proteases by identifying compounds capable of inhibiting the catalytic activity in a method wherein the protease is combined with a candidate inhibitor and a chromogenically- or fluorogenically-labeled peptide substrate in solution and the change in the color or fluorescence resulting from cleavage of the substrate is

measured to identify inhibitors of the protease. In view of the motivation provided by Cohen et al., it would have been obvious to one of ordinary skill in the art to follow the teachings of Bang et al., Kopetzki et al., Moloney et al. and Kuhn et al., and prepare an expression vector comprising a fusion polypeptide-encoding polynucleotide providing nucleic acid sequence regions encoding signal and propeptide sequence regions and an in-frame cloning site for the insertion of a sequence encoding a human S1 protease catalytic domain as well as a further coding sequence specifying a polyhistidine tag to facilitate the purification of the expressed and processed catalytic domain of the fusion polypeptide, and to express, process, and recover the human S1 protease catalytic domain to discover inhibitors of human S1 serine proteases.

One of ordinary skill in the art would have had a reasonable expectation of success at the time the invention was made in preparing such an expression vector to express, process, and recover a human S1 protease catalytic domain with which to discover physiologically active inhibitors in a method of detection using chromogenically- or fluorogenically-labeled peptide substrates because expression vectors designed for the expression of a zymogen comprising a propeptide and a heterologous protease catalytic domain, and subsequent processing and isolation of the protease catalytic domain, were well-known in the art, and in use in the art, as evidenced by the teachings of Bang et al., Kopetzki et al. and Moloney et al., and because Kuhn et al. teach that providing an additional polyhistidine "tag" in a fusion polypeptide facilitates rapid purification of a desired recombinant expression product in a highly purified state, which such an artisan at that time would have appreciated as useful in a method for detecting compounds that are physiologically active inhibitors of a human S1 serine protease.